Patent Office on February 10, 1993. Claims 1 to 6, 8 and 15 to 18 are therefore presently pending in the application.

Claim 18 has been amended according to the suggestion of the examiner to correct a typographical error.

In the Office Action of June 7, the rejection of all of the pending claims under 35 U.S.C. §103 was reiterated and made final. In addition, the examiner indicated that the applicants' arguments of February 10 and the Aberg Declaration submitted therewith were not persuasive.

In the new discussion in paragraph 6 of the Office Action, the examiner states "Note the summary of the Brittain et al article regarding the desirability of using the R(-) isomer and its effects on β-adrenoreceptors." The Summary section in the Brittain reference does not address the "desirability" of using the R-isomer; it states that the R-isomer is more potent. Applicants have previously explained that potency does not equate with desirability; other factors must be considered. (E.g., Chloramphenicol is more potent than penicillin V, but in most cases it is not more desirable.)

Moreover, it is not understood by applicants why the teachings of Brittain are isolated and emphasized by the examiner when the equally valid teachings of Hartley and Middlemiss are available which show that the racemate is 1.5 times as potent as the R-isomer. The analysis of selected pieces of the art has been found improper by the CCPA in *In re Kuderna* (165 USPQ 575). The issue of patentability must be approached "in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all the relevant teachings in the art." [Emphasis in original] In the previous response, applicants have analyzed the teachings of the art taken as a whole; the substance of that response is summarized below.

The thrust of applicants' invention is the reduction of side effects, which arise in the treatment of asthma with racemic albuterol, by the administration of R-(-)-albuterol in place of

racemic albuterol. Side effects of drugs which, like albuterol, have a predominant β_2 agonist component, can arise from a number of interactions, one of which is addressed by the cited prior art: interaction of the primarily β_2-agonist drug with β_1 receptors. The Brittain, Hartley, Hawkins and Buckner references address the comparative interaction of albuterol isomers with β_1 vs β_2 receptors. None of the references shows that there is any β-selectivity advantage of R over S or over racemic. On the contrary, Buckner concludes that the ratios of tracheal (β_2) to atrial (β_1) activities of R and S are indistinguishable. The earlier Aberg Declaration confirmed that the references by Brittain, Hartley, Hawkins and Buckner do not teach any expectation of decreased side effects from the administration of the pure R isomer as compared to the racemate.

Thus, at the time of filing of applicants' parent application (1/5/90), the references cited would not have motivated a person of ordinary skill to administer the pure R(-) isomer of albuterol for the treatment of asthma on the basis of its receptor selectivity.

The examiner has suggested that increased potency might be a basis for separating enantiomers. However, to the contrary, and mindful that applicants' disclosure does not relate to potency, the art does not encourage the artisan of ordinary skill to resolve and administer pure R albuterol on the basis of potency. The reason for this lack of encouragement is because the theoretical advantage of a pure enantiomer is at most two-fold. A racemate, being a 50:50 mixture, simply acts like half a dose of the pure enantiomer and half a dose of filler. Since chemical resolution of racemic mixtures is never 100% efficient, a resolution will always yield less than 50% of the single isomer. Thus, unless one enantiomer antagonizes the effect of the other, there is no potency-based reason to suffer the loss of material attendant upon their resolution.

A potency ratio significantly greater than 2 between a

single enantiomer and its racemate would be consistent with antagonism by one enantiomer and would provide motivation for resolving the racemate. No such teaching is found in any of the references. Therefore, at the time of filing, the art did not suggest using pure R(-) albuterol either for lessened side effects or for potency enhancement. This conclusion was supported by the earlier Declaration of Dr. Aberg.

The examiner has suggested that applicants show comparative therapeutic indices to support their contention of lessened side effects. Applicants provide herewith the Declaration of Dr. Gunnar Aberg to establish that the results of Chapman and of Morley, in view of additional studies now performed by applicants, would indicate to the person of skill in the art that the R-isomer would have a higher therapeutic index in humans than would the racemate. The tests are accepted in the art as being predictive of efficacy in treating humans, and the pending method of use claims are narrowly drawn to the specific use for which the tests are predictive. (See *Ex parte Chwang*, 231 USPQ 751). Thus, as a matter of law, an adequate showing has been made to support patentability of the pending claims.

The examiner has further cautioned the applicants that a showing, if made, might not be persuasive in light of *In re Adamson*. In *Adamson*, the CCPA held that in establishing that one isomer was more potent, the applicants had "done no more than is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art." [Emphasis added] In the present case, applicants have shown that the art, taken as a whole, does not suggest that the resolution of the racemate and the use of R-(-)-albuterol substantially free of its S-isomer would provide therapy for asthma while simultaneously reducing side effects. Thus, the demonstration of improved therapeutic index by applicants should be persuasive in light of *In re Adamson*.

For the above stated reasons, applicants believe that the rejections under 35 U.S.C. §103 have been overcome. Applicants

respectfully request reconsideration of the application and allowance thereof. If the examiner feels that a telephone conversation would expedite prosecution of this application, he is asked to call applicants' agent at (617) 861-6240.

Respectfully submitted,

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